

Sub E2

where not more than one polymer molecule is covalently attached to said the monovalent antibody fragment, said polymer molecule is linked to said cysteine residue in said hinge region of said heavy chain; and wherein said polymer is an optionally substituted, straight or branched chain polymer selected from the group consisting of poly(ethylene glycol), poly(ethylene glycol), poly(propylene glycol), poly(vinyl alcohol) and derivatives thereof.

ADD E3

Remarks

Preliminarily, Applicants note with appreciation that the following rejections have been withdrawn: the rejection of claims 1, 5, 9-11 under 35 U.S.C. § 112, second paragraph; the rejection of claims 1, and 9-11 under 35 U.S.C. § 102(b) over Pedley et al.; and the rejection of claims 1, 5 and 9-11 under 35 U.S.C. § 103(a) over Pedley et al., in light of Goodson et al. and Woghiren et al.

I. Claim Amendments

Claims 1, 5, 9-11 were pending in this application. Claim 1 has been cancelled without prejudice. Applicants reserve the right to pursue the subject matter of this claim in a continuing application. Claim 12 has been added. Claims 5, 9-11 have been amended. Claims 5, 9-12 will be pending after this amendment. In view of the foregoing amendments, and arguments that follow, Applicants respectfully request withdrawal of the rejections upon reconsideration.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

II. Rejections under 35 U.S.C. § 102(e)

Claims 1 and 9-11 remain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Griffiths et al. (U.S. Patent 5,670,132). Allegedly, Griffiths et al. describes monovalent antibody fragments which can be PEGylated to a thiol group in the hinge region. Claim 1 has been cancelled and claim 12 has been added. To the extent that this rejection is levies against the amended claims, Applicants respectfully traverse the rejection.

Griffiths et al. does not describe all of the elements of new claim 12. New claim 12 recites an antibody fragment which has a hinge region which comprises not more than one cysteine residue, and has not more than one polymer molecule covalently attached, where the polymer molecule is covalently attached to the single hinge cysteine residue. Support for claim 12 is found. e.g., in the Examples where it is disclosed that human monoclonal antibodies hA5B7, hTNF40 and hg162 have been engineered to have only one cysteine in the hinge region available for PEGylation (see, for example, page 13, lines 21-32, page 14, lines 4-7; and generally, page 5, line 30 to page 6, line 10 of the application as filed).

Griffiths et al. does not disclose or suggest an antibody fragment with only one polymer molecule covalently attached, where the hinge region comprises not more than one cysteine residue, and where the hinge cysteine residue is covalently attached to the polymer molecule. Nor does Griffiths et al. provide a working example of pegylation of the thiol groups. This description is provided prophetically and confusingly. Griffiths et al. suggests the following procedure for preparing

antibody fragments that are PEGylated on thiol groups **but** which retain disulfide bonds to bind to Tc-99m after reduction.

1. PEGylation of intact immunoglobulin following partial reduction under mild conditions;
2. purifying PEG-antibody conjugates by size exclusion chromatography;
3. digesting the PEG-antibody conjugates with pepsin or papain; and
4. reducing the PEG-antibody to produce free thiols again for labelling with Tc-99m.

Regarding Step 4, Griffiths et al. discloses that the disulfide bonds in the **hinge** region are generally more accessible to disulfide reducing agents and can be selectively cleaved (Griffiths et al., col. 4, lines 56-58). As questionable as this procedure is (i.e., which thiol groups are PEGylated in Step 1?), Griffiths et al. clearly contemplates a hinge cysteine being available **after** PEGylation for Tc-99m labelling. This is distinct from Applicants' invention as presently claimed.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

III. Rejections under 35 U.S.C. § 103(b)

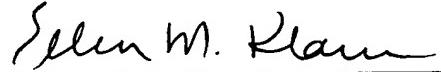
Claims 1, 5 and 9-10 remain rejected under 35 U.S.C. §103(b) as allegedly unpatentable over Griffiths et al. in further view of Goodson et al. or Woghiren et al. Claim 1 has been cancelled. Claim 12 has been added. Neither Griffiths et al., Goodson et al. nor Woghiren et al. disclose or suggest, individually or in combination, the antibody fragment of new claim 12.

Neither Griffiths et al., Goodson et al. nor Woghiren et al. disclose or suggest, individually or in combination, an antibody fragment with not more than one covalently attached polymer molecule, where the hinge region comprises not more than one cysteine residue and where the hinge cysteine residue is covalently attached to the polymer molecule. As discussed above, discussion incorporated herein, Griffiths et al. does not disclose or suggest Applicants' invention. The remaining references do not overcome this deficiency. Goodson et al. and Woghiren et al. allegedly describe a protein modified with the addition of methoxy(polyethylene glycol) to cysteine residues in the protein. Neither Goodson et al. nor Woghiren et al. describe or suggest PEG-labelled antibody fragments. Thus, the references do not, alone or in combination, yield Applicants' invention, nor is there any motivation to modify them to do so.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C § 103 be withdrawn.

For the foregoing reasons, Applicants submit that the present claims meet all the requirements for patentability. The Examiner is respectfully requested to allow all the present claims. If the Examiner is of a contrary view, he is requested to contact the undersigned at (215) 557-5948.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE**In the claims:**

Claim 1 has been cancelled.

5. (Twice amended) An antibody fragment according to ~~claim 1~~ claim 12 wherein the polymer is selected from the group consisting of methoxy(polyethylene glycol) and derivatives of methoxy(polyethylene glycol).

9. (Amended) An antibody fragment according to ~~any one of Claim 1 to Claim 8~~ claim 12 covalently attached to one or more effector or reporter molecules.

10. (Amended twice) A composition comprising a monovalent antibody fragment according to ~~any of the preceding claims~~ claim 12 together with one or more pharmaceutically acceptable excipients, diluents or carriers.

11. (Amended) The monovalent antibody fragment of ~~claim 1~~ claim 12, wherein the antigen-binding fragment is selected from the group consisting of an Fab fragment and an Fab' fragment.

The following claims have been added:

12. (New) A polymer modified monovalent antibody fragment, wherein said antigen-binding fragment comprises a heavy chain and a light chain, wherein said heavy chain comprises of a V_H domain covalently linked at its C-terminus to a C_H1 domain extended to provide a hinge domain, said hinge domain comprising not more than one cysteine residue;

said light chain comprising of a V_L domain, which is complementary to the V_H domain, covalently linked at its C-terminus to a C_L domain;
where not more than one polymer molecule is covalently attached to said the monovalent antibody fragment, said polymer molecule is linked to said cysteine residue in said hinge region of said heavy chain;
and wherein said polymer is an optionally substituted, straight or branched chain polymer selected from the group consisting of poly(ethylene glycol), poly(ethylene glycol), poly(propylene glycol), poly(vinyl alcohol) and derivatives thereof.